ACUTE AND DELAYED EFFECTS OF MELATONIN : OPERATIONAL SIGNIFICANCE

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Summary
The primary function of melatonin in mammals is to convey information about the changing length of the night in the course of the year. Melatonin appears not to be essential for circadian organisation but reinforces functions associated with darkness. In diurnal humans this of course included sleep and lowered body temperature. It may act as an adjunct to light for the maintenance of synchrony with the solar day. Exogenous melatonin can both advance and delay the timing of sleep and other circadian functions and appears to stabilise sleep to a 24h period taken daily at an appropriate time in free running conditions. However there is at yet little evidence that it can consistently synchronise free running strongly endogenous variables such as core temperature. Its effects on sleep in free run are complex, depend on circadian time of administration, and in part can be interpreted on a photoperiodic basis.

Introduction
In all eukaryotic species from microorganisms to humans melatonin is normally synthesized during the night (1) and its duration of secretion reflects the length of the night. In mammals its primary sites of production are the pineal gland and the retina, where it is derived from tryptophan via acetylation of serotonin to N-acetylserotonin and O-methylation of the latter to N-acetyl-5-methoxytryptamine (melatonin). The rhythm of pineal synthesis is generated in the suprachiasmatic nuclei (SCN) and synchronized to the 24h day primarily by the light dark cycle. In healthy volunteers the production in terms of amplitude, detailed profile and phase is very stable in the same individual from day to day. The rhythm is closely coupled to that of core body temperature. In humans the peak of melatonin and the nadir of temperature are in close coincidence and this relationship may be in part causal. The relationships of many sleep parameters to the core temperature nadir can thus in principle be applied to the peak of melatonin. The primary physiological function of melatonin is to transduce photoperiodic information for the organisation of seasonal and circadian physiology.

A number of drugs (1), posture (2) and exercise (3) will modify melatonin secretion, and sufficiently bright light will suppress production at night (4). However if these are controlled it is assumed, not unreasonably, that the phase of melatonin, or its urinary metabolite 6-sulphatoxymelatonin (1) reflects the phase of the endogenous clock in the SCN. This has led to the extensive use of melatonin as a 'circadian marker rhythm'.

The actions of melatonin as a possible endogenous circadian zeitgeber in humans have been much discussed (e.g. 5). Since its profile of secretion depends essentially on the light dark cycle it can only function endogenously as an adjunct to light in sighted humans. It has also been proposed as an endogenous sleep substance, as an opener of the 'sleep gate' in the evening, as 'nature's soporific' (6, 7, 8, 9). It is difficult to understand how a

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substance which is made at night in all species including nocturnal species can be 'natures soporific'- indeed this is the strongest possible argument against a universal sleep promoting role for melatonin.

Melatonin and sleep

Humans can sleep out of phase with endogenous melatonin, although their sleep may be shorter, have more wakefulness and be subjectively of poorer quality than when sleeping in phase (10, 11). It is remarkable that some free running blind subjects, whose peak melatonin will intermittently occur, depending on endogenous periodicity (tau), during the daylight hours, do not complain of sleep problems (although many others have sleep disorders related to free running rhythms), (12, 13, 14). Some of the best correlative evidence concerning an endogenous role for melatonin in human sleep comes from studies in free running blind or sighted subjects when maximum sleep propensity occurs closely associated with the peak of melatonin secretion and the trough of core temperature (15). In the case of blind subjects living in a normal environment this is particularly evident by the occurrence of daytime naps when melatonin peaks during the day (13). Further elegant correlative data from Lavie and co-workers suggests that the evening melatonin rise may open a 'sleep gate' (7).

Acute effects on sleep

There is no doubt that melatonin does affect sleep. The first evidence dates from 40 years ago when Aaron Lerner, who first isolated the substance, took 100 mg and described sleepiness after the dose (16). Early investigations used electroencephalographic (EEG) characteristics to delimit an acute mild sedative and 'hypnotic' effect in both animals (cats, rats, chickens) and humans, reviewed by Cramer in 1974, (17). Subsequently a substantial literature, generally using much lower doses, has described advance shifts in the timing of sleep after early evening administration, transient sleepiness at several different times of day within 2-4h of the dose, time dependent increases in sleep propensity, effects on the waking EEG comparable to, but not identical with, benzodiazepines, a lengthening of the first rapid eye movement (REM) episode after early evening administration, increases in the fast EEG frequencies after evening naps or night time sleep and 'beneficial effects' taken at bedtime. The latter are usually a reduction in wake after sleep onset (WASO) and an increase in total sleep time (TST) evaluated subjectively, by actigraphy and, rarely, by EEG. When melatonin was used to hasten adaptation to a 9h phase advance, TST, sleep efficiency and stage 2 sleep were increased whereas slow wave sleep (SWS) was decreased (18), but only on the first post phase shift day. The subject has been extensively reviewed recently (7, 19, 20, 21, 22). There is still inconsistency in the findings however and some studies have found no effects of any importance on sleep (e.g. 23). Differences between study conditions, subjects, dose and timing are likely to be the reason for apparently contradictory effects and much more information is needed for solid conclusions to be drawn.

Phase shifting effects of melatonin

Following an acute dose of melatonin (0.5 -10 mg) core body temperature declines and causal links have been suggested between this effect, the induction of sleepiness and, in the case of early evening administration, earlier sleep and a subsequent phase advance of melatonin onset (24, 25, 26, 27). Substance has been added to this speculation by the observation that both the temperature decline and the sleepiness are dependent on posture. Subjects who remain upright and/or active after the dose do not show either the sleepiness or the temperature drop (28). However the induced phase shift may not depend on changes in core temperature. In early work, subjects taking 2mg melatonin daily at 1700h for 30 days and remaining active only showed significant evening sleepiness after 4 days as a group (29, 30). Moreover in conditions where very little acute change in temperature was found, phase shifts still occurred (31).

It is our opinion that endogenous melatonin indicates dark onset (the rise) and offset (the decline) and reinforces physiological functions associated with darkness in humans as in other mammals. Pharmacological doses of melatonin may well act differently. What constitutes a physiological dose of melatonin remains problematic. In the authors' experience fast release doses of melatonin in corn oil/1% ethanol from 0.05 - 0.2 mg give, on average, 'physiological', i.e. night time plasma concentrations of melatonin during the day (24). Individual pharmacokinetics are extremely variable with plasma levels varying up to 25 fold and this may account for some of the variability in the literature (32, 33). For example even 2 mg can give rise to near physiological levels in a very few individuals

(30, 33). Evidently what is a physiological dose is individually variable.

Fast release melatonin (0.5 mg - 5mg, or less in divided doses) phase advances and delays the circadian system (endogenous melatonin, core temperature, sleep timing) according to a PRC (31, 34, 35, 36). In our experiments this is a dose related phenomenon for advance phase shifts in the range 0.05-5mg (24). The duration of endogenous melatonin may be increased by evening oral administration since the onset can be advanced more than the offset (30, 37), and in large enough doses the morning decline may be delayed. In this way the circadian and photoperiodic effects become confounded, if indeed they are distinguishable at all.

Delayed effects of melatonin: synchronisation of human circadian rhythms

Since melatonin does show the characteristics of a zeitgeber in that a PRC can be generated, it would be expected to entrain fully the circadian clock in suitable circumstances. Human tau appears to be on average 24.3h or less in constant dim light in sighted subjects (38, 39, 40) and thus the clock needs to be phase advanced on average by 0.3h or less each day. Acute phase shifts induced by melatonin in an entrained or free running environment are of at least this magnitude when sleep is permitted. However it is difficult to demonstrate entrainment in humans, with the exception of apparent entrainment ('stabilisation to 24 hours') of the sleep wake cycle (31, 41, 42, 43). Given to blind subjects free running in a normal environment melatonin (5mg) induces phase shifts and can stabilise sleep (especially sleep onset) in some subjects (42, 43). Very recent data using carefully timed melatonin shows that the circadian system can indeed be fully entrained in some but not all blind individuals (Lockley, Skene, Arendt, submitted for publication).

It is possible to maintain the circadian system of the majority of sighted subjects transferred to a free run in constant dim light (<8 lux) on a cycle indistinguishable from 24h by daily administration of melatonin (5 mg, 2000h) at 24h intervals for periods of 15 days (31). Less successful was an attempt to reentrain the same subjects after free running with different periodicities for 15 days in constant dim light by daily melatonin at the same clock time. The initial melatonin administration at 2000h occurred at different circadian phases. Both phase advances and phase delays of sleep and core temperature were seen according to a PRC. However the data indicated that the effects observed were complex and variable. Some subjects showed a stabilization of sleep onset with little effect on sleep offset for periods of several days. There was some evidence for splitting of sleep such that some components delayed and others advanced to resynchronise. One subject showed a double phase delay and sleep (but not core temperature) appeared to entrain to melatonin given at sleep offset for several days. Core temperature data indicated that tau was shortened, in one case to significantly less than 24h, rather than fully entrained, in many subjects. Since the time series was short (15 days) some taus indistinguishable from 24 h may well not have been synchronised. Similarly a longer study time might have shown synchronisation of temperature in more subjects. Only a very long time series would resolve these questions.

Most surprising of all in this free running study was a phenomenon of fragmentation of sleep in two subjects taking 5mg melatonin close to core temperature maximum immediately after transferring to a dim light environment. Cross-over from melatonin to placebo led to consolidated sleep. A subsequent attempt to time melatonin specifically to be close to core temperature maximum provided two further subjects showing fragmented sleep with melatonin compared to placebo (44). Thus, of a total of 16 subjects studied in dim light in this way, 4 showed sleep fragmentation. There was evidence by spectral analysis for the presence of two components with different periodicities in 3 of the 4 subjects.

Whatever the explanation it is clear that this phenomenon would be highly undesirable if consolidated sleep and alertness is required. However a strategy of splitting sleep into two components with melatonin may lead to more rapid adaptation to phase shift by advance of one and delay of the other component.

Melatonin can however maintain apparent entrainment (stabilisation to a 24 hour period) of sleep in most individuals. This may simply be a masking effect of acute sleepiness induced by the treatment. But some data is inconsistent with this hypothesis. Notably the fragmentation of sleep by melatonin in some free running individuals, as described above, is evidence against strong acute hypnotic effects. Similarly, taken during free running experiments during periods of minimum sleep debt, sleep does not necessarily follow the

treatment. The data in this case are more consistent with an effect on sleep timing. Since sleep can be apparently entrained in the absence of temperature entrainment this suggests that the mechanisms of sleep timing differ from those of strongly endogenous rhythms such as temperature. The differentiation of the central circadian clock in the SCN into discrete areas and the fact that SCN cells in culture each show individual periodicities supports this possibility (45, 46, 47).

Conclusions

The majority of published data indicate that melatonin has therapeutic benefits in circadian rhythm-related sleep disorders and adaptation to forced phase shift (22). However as yet its mechanism of action remains unclear, the appropriate dose for any given condition and individual is uncertain, the contraindications remain to be defined, there is virtually no data on long term safety, use with concomitant medication or organic disease and very little information concerning its most important function as a photoneuroendocrine transducer in humans. Since it appears to have some photoperiodic effects, and since in principle daylength has the potential to affect many if not all physiological systems, much further research is needed on its physiological role and pharmacological effects in humans.

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